Case Report

Low-dose Cyclophosphamide-induced hepatotoxicity in a multiple sclerosis patient: A case report and literature review
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ABSTRACT
Cyclophosphamide (CTX) is an alkylating agent commonly used to treat malignancies and immune-mediated inflammatory nonmalignant processes. It is used off-label for multiple sclerosis (MS) treatment as a disease-modifying therapy (DMT). Acute adverse effects include bone marrow suppression, hemorrhagic cystitis, nausea, vomiting, and hair loss. Hepatotoxicity with high dose CTX is well recognized but low dose CTX induced hepatitis has rarely been described.

We report a case of a 28-year-old woman with MS who developed acute icteric hepatitis within 8 weeks of receiving low dose intravenous CTX and methylprednisolone (MP). Liver biopsy showed liver cell necrosis. CTX and steroid treatment were discontinued, and her symptoms and laboratory tests improved. Steroids were reintroduced without relapse; the evolution was favorable with liver enzymes normalization.

To the best of our knowledge, this is the first report of acute cholestatic hepatitis developing after administration of low-dose CTX in MS patient. We may suggest that baseline liver function tests and periodic assessment should be monitored during CTX treatment.

Key words: Cyclophosphamide, Hepatotoxicity, Multiple Sclerosis

INTRODUCTION
Cyclophosphamide is a synthetic nitrogen mustard-like alkylating agent indicated for the treatment of malignancies and nephritic syndrome. It is used off-label for the treatment of many diseases, including MS and lupus nephritis. Reported side effects include bone marrow suppression with opportunistic infections, hemorrhagic cystitis, temporary infertility, nausea, vomiting and hair loss. In fact, hepatotoxicity with high-dose CTX is well recognized, but hepatitis due to low dose CTX has rarely been described.

We hereby report a case of acute icteric hepatitis following a short course of low-dose CTX in a young woman with MS. To the best of our knowledge, this is the first reported case of low-dose CTX-induced hepatotoxicity in a MS patient.

CASE REPORT
A 28-year-old African female was referred to our unit in November 2016 for a recent onset of acute jaundice. Eight weeks prior to this presentation, she was diagnosed with remitting MS on the basis of clinical and radiological findings. The patient received IV CPM (1g) and IV MP (1g) every four weeks for 3 months. She had no history of liver disease, alcohol intake or risk factors for viral hepatitis. She wasn’t taking any other medications or herbal preparations. She was icteric with dark urine and pale stools. Body temperature was 37.2°C. There was no abdominal tenderness or any sign of chronic liver disease in the physical examination.

Laboratory findings showed hyperbilirubinemia 159 mg/dl, normal indirect bilirubinemia 4.9 mg/dl, liver cytolysis with markedly elevated alanine aminotransferase 475 UI/l (Nx10.3) and aspartate aminotransferase 350 UI/l (Nx10) with mild increase in alkaline phosphatase 177 U/L (Normal 105) and gammaglutamyl-transpeptidase GGT 45 U/L (Normal 38). Total protein, albumin, gammaglobulines, coagulation times, serum creatinine and C-reactive protein were unremarkable. Blood and platelet counts were normal. An abdomen ultrasound showed no biliary obstruction or signs of cirrhosis or portal hypertension. Viral hepatitis (A, B, C) were ruled out by appropriate virologic tests. Autoimmune screening (Anti-mitochondrial M2-antibodies, anti-liver-kidney microsome antibodies, anti-smooth
Within 2 weeks, jaundice probably induces sinusoidal obstruction syndrome, leading to a direct toxic effect on sinusoidal cells in the liver, thereby causing necrosis, obstruction, and obliteration of hepatic veins.

**DISCUSSION**

Herein we report the first case of acute icteric hepatitis after low-dose IV CTX for MS. CTX is a synthetic, nitrogen mustard-like alkylating agent that requires hepatic metabolism for activity. The major safety issues that have been associated in MS patients include bladder cancer and gonadal toxicity. Portaccio et al evaluated 112 patients with MS who received pulse CTX of 700 mg/m2 monthly for 12 months then bimonthly for 12 months. Serious side effects happened in 21.4% of patients and included: amenorrhea, hypogammaglobulinemia, hemorrhagic cystitis and malignancies. Perini et al. concluded that using the usual MS protocol, the most common side effects were mild alopecia, nausea, vomiting and cystitis.

**Patient details**

A 67-year-old woman who developed acute liver injury with jaundice 8 weeks after starting oral CTX (100 mg daily) for nephrotic syndrome thought to be due to lupus erythematosus. CTX was discontinued and her liver test abnormalities improved rapidly.

**CONCLUSION**

Hepatotoxicity may occur even after low-dose IV CTX treatment. Physicians should be aware of this potentially serious adverse effect.
adverse reaction and should not reintroduce CTX after hepatotoxicity caused by the first dose. We may suggest that initial and follow-up liver function tests should be done and monitored in all patients receiving this chemotherapy.

DISCLOSURE

The authors report no conflicts of interest in this study.

REFERENCES

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